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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,200	04/07/2004	Henrik Bisgard-Frantzen	5835.210-US	7464

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EXAMINER	
MONSHIPOURI, MARYAM	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/820,200	BISGARD-FRANTZEN ET AL.	
	Examiner	Art Unit	
	Maryam Monshipouri	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 31-48 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 31-48 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/710,339.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 1-30 have been canceled. Claim 31-48 are still at issue and are present for examination.

Applicants' arguments filed on 10/10/2005 have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-48 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for variants of SEQ ID NO:2 as recited in claim 31 with amylase activity, does not reasonably provide enablement for variants of SEQ ID NO:2 as recited in claim 31 having at least 70-99% identity to said amino acid sequence while retaining fungamyl-like alpha-amylase activity according to the previous office action.

In traversal of this rejection applicant argues that homology of a variant alpha amylase of SEQ ID NO:2 to the parent alpha amylase may be determined for example by means of computer programs known in the art, such as GAP provided in GCG program package and there is an extensive body of patent and scientific literature relating to alpha amylases, including SEQ ID NO:2.

That the specification also provides detailed guidance for identifying suitable amino acid residues for modification in variants of SEQ ID NO:2. According to applicant the three-dimensional structure of the alpha amylase of SEQ ID NO:2 is known. This structure is a useful tool for an artisan to determine which additional residues can be altered and which amino acids should be conserved to practice the claimed invention.

The identification of specific positions or regions to be mutated on variants of SEQ ID NO:2 in order to obtain improved thermostability may be achieved by using molecular dynamics simulations to find regions having the highest mobility or flexibility. Substitutions may be directed against residues in these regions. The specification further teaches processes such as site directed mutagenesis for producing alpha-amylase variants related to SEQ ID NO:2 that fall within the claimed invention. Thus, it would be routine for the skilled artisan to make three claimed variants commensurate with the scope of the invention and hence, the rejection should be withdrawn.

These arguments were fully considered but were found **unpersuasive**. This is because even though the examiner agrees with the applicant that methods for producing amylase variants such as site directed mutagenesis are well established in the prior art and by using a computer program and the dimensional structure of amylase in some cases one can predict which regions of the parent amylase should be mutated without affecting activity , she still maintains that in the instant case it is undue experimentation in order to prepare variants of amylase variants having at least 70% identity to SEQ ID NO:2 comprising an alteration in regions 98-110 and 16-167 wherein

each region or position corresponds to the amino acid sequence of the parent amylase having SEQ ID NO:2.

Applicant is reminded that in claims 42-48 the parent fungamyl alpha amylase is no longer SEQ ID NO:2 but needs to only retain 70-99% sequence identity to SEQ ID NO:2. Hence, the claimed variants comprise mutations (i.e. substitutions, deletions or insertions) everywhere including regions 98-110 and 161-167 of the variants of 70% or higher homologs of SEQ ID NO:2, while maintaining amylase activity. The specification fails to provide any guidance or examples as how to identify corresponding regions to those regions recited in claim 31, in the 70% or higher identity homologs of SEQ ID NO:2, wherein the parent alpha amylase has been mutated for example by deletions. The prior art teaches that once the structure of a parent amino acid sequence is modified, by specially deletion or insertion, as is the case with SEQ ID NO:2 variants of 70% or higher it is no longer possible to identify corresponding regions or positions to the parent amino acid sequence for further mutations (i.e deletions, substitutions etc.). Thus, at such situation preparation of variants of claims 42-46, if not impossible in the least **does impose an undue burden of experimentation on the skilled artisan.**

Therefore, based on the response provided above in addition to explanation provided previously the examiner finds no reason to drop the rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 42-48 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 42-48 are directed to a **genus** of alpha-amylase homologs that have been inadequately described in the specification as stated in the previous office action.

In traversal of this rejection applicant argues the following: that the Federal circuit recently discussed that "it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim provided the effect is sufficiently demonstrated to characterize a generic invention. Again applicant emphasized that there is an extensive body of patent and scientific literature relating to alpha amylases.

The specification describes many alpha amylases variants falling within the claimed invention that an artisan can use to practice the claimed invention. The specification also provides detailed guidance for identifying other alterations that can be made, using for example the 3 dimensional structure of SEQ ID NO:2 and molecular dynamics simulations to identify suitable amino acids for modification in variants of SEQ ID NO:2. Therefore in view of applicant sufficient support is provided for alpha amylase variants of at least 70% identity to SEQ ID NO:2 within the scope of the claims and it is not necessary to disclose the structure of all variants that fall within the claimed

invention to demonstrate that applicants were in possession of the invention at the time the application was filed and therefore the rejection should be dropped.

Once again these arguments ere fully considered but were found **unpersuasive**. The examiner respectfully requests applicant to examine the scope of the genus claims 42-46 directed to variants of variants of SEQ ID NO:2. The examiner cannot agree with the applicant that the claimed invention is "generally operable" and hence, the discussion of the Federal circuit decision is not relevant to the claimed invention. As stated above, in claims 42-46 the **genus** of parent fungamyl alpha amylases needs to only retain 70-99% sequence identity to SEQ ID NO:2. Hence, the claimed variants are directed to a genus of polypeptides that comprise mutations everywhere including regions 98-110 and 161-167 direted to a genera of variants of 70% or higher homologs of SEQ ID NO:2, while maintaining amylase activity.

Considering the breadth of the claims directed to variants or SEQ ID NO:2 variants, even though the techniques for preparation of mutants by site directed mutagenesis are well established and the three dimensional structure of SEQ ID NO:2 are available, some crucial information with regards to identification of "corresponding regions or positions" to active variants of 70% or higher identity to SEQ ID NO:2 prepared by specially, deletion or insertion mutations is necessary that is currently lacking in the specification and providing a **single species** namely SEQ ID NO:2 cannot lead the skilled artisan to a reasonable conclusion the applicant had possession of the invention.

Therefore, based on the response provided above in addition to explanation provided previously, the examiner finds no reason to drop the rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Christenson (cited previously), in view of Matsuura (cited previously) further in view of Svendsen (cited previously) as stated in the p[previous office action.

In traversal of the rejection applicant argues the following :(1) that none of cited references teach or suggest the variant fungamyl-related alpha amylases. Christenson is directed to bacterial enzyme and methods of producing the same. Matsuura discloses fungal alpha amylases but does not teach or suggest the alterations recited in the represent claims and Svendsen is directed to bacterial related alpha amylase variants.

(2) That the alterations of Svendsen are based on the aspects of bacterial related alpha amylases which have very low identity to fungamyl related alpha amylases of the present invention. Further, Svendsen specifically states that the variants it describes are based on some striking and not previously predicted difference between "the termamyl-like alpha amylase structure and both fungal and mammalian alpha amylase. Therefore in view of applicant Svendsen alone or in combination with Christenson and Matsuura

does not suggest the alterations in fungal-related alpha amylases as claimed instantly and therefore the rejection should be withdrawn.

These arguments were fully considered but were found **unpersuasive** for the following reasons: In response to applicant's **first** argument, the examiner agrees with applicant that none of said reference alone teach the claimed invention and it is for that reason that said references were not cited as 102 art against the claimed invention. Further, as applicant herslef/himself admits in the response to 112 first rejections, it is not necessary that said alterations to be explicitly taught in the cited art because based on computer analysis and availability of crystal structures of bacterial (Termamayl) and fungamyl alpha amylases one of ordinary skill can reasonably predict those alterations, as explained in the previous office action.

With respect to applicant's **second** argument the examiner respectfully disagrees with the applicant that all Svendsen alterations are based on some sticking and not previously predicted differences between bacterial and fungal alpha amylases. Applicant is respectfully requested to read Svendsen patent again or at least consider the quote from page 3 lines 13-18 of Svendsen shown below:

"... when comparing the Termamyl-like alpha amylase with known structures of the fungal and mammalian alpha amylases mentioned above, it has been found that some similarities exist between the structures, but also that some striking, and not previously predicted structural differences between the alpha amylases exist. The present invention is based on these findings."

To the understanding of the examiner Svendsen in the above quote is referring to alterations to both similar and different regions of said amylases and not just alterations in areas of dissimilarity.

Further, low sequence identity between bacterial and fungal alpha amylases by itself does not bar prediction of regions in which alterations may result in predictable change in enzyme property. Rather, as applicant is well aware, it is the enzyme two and three dimensional structure in combination with its amino acid sequence that allows or bars prediction of regions in which alterations affect enzyme property.

Furthermore, even if for the sake of argument, one assumes that all alterations of Svendsen in bacterial like (Termamyl-like) amylases were done in regions of dissimilarity between fungal and bacterial alpha amylases, enhanced thremostabiliy requires that bacterial (Termamyl-like) alpha amylase which lacks sufficient thermostabilty to be altered towards fungal amylase structure, which is more thermostable, which is more thremostable. Hence, finding equivalent regions for alteration in instant amylase based on the teachings of Svendsen may be interpreted as a thermostability optimization effort, resulting in identification of specific substitutions in fungamyl amylase by even more desirable amino acids than those in the wild type enzyme to further enhance the themostability of parent fungal amylases and such findings or optimization efforts are always motivating by one of ordinary skill in the art.

In conclusion, the rejection is maintained based on the above response in addition to those provided in the previous office action.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maryam Monshipouri whose telephone number is (571) 272-0932. The examiner can normally be reached on 7:00 a.m to 4:30 p.m. except for alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Weber Jon P. can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/M. Monshi/

Maryam Monshipouri Ph.D.

Primary Examiner

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